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Concentration and Variability of Urinary Phthalate Metabolites, Bisphenol A, Triclosan, and Parabens in Korean Mother–Infant Pairs

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Abstract: Concentrations of toxic chemicals in mothers highly correlate with those in their children; moreover, the levels are higher in children than in mothers. Non-persistent chemicals with a short half-life including phthalate metabolites, bisphenol A (BPA), triclosan (TCS), and parabens are metabolized and excreted through urine. Therefore, we assessed the urine concentrations of phthalate metabolites, BPA, TCS, and parabens; correlated the concentrations with exposure levels; and assessed the within-individual variability of these chemicals in mothers and their infants. We collected 225 and 71 samples from 45 mothers and 36 infants, respectively. For the variability analysis, 189 and 42 samples were collected from nine mothers and their infants, respectively. The median concentrations of phthalate metabolites in the mothers and infants were 0.53–26.2 and 0.81–61.8 μg/L, respectively, and those of BPA, TCS, and parabens were 0.24–76.3 and 2.06–12.5 μg/L, respectively. The concentrations of monoethyl phthalate (MEP), mono-N-butyl phthalate (MnBP), mono-isobutyl phthalate (MiBP), and BPA in the mothers were positively correlated with those in infants (0.45, 0.62, and 0.89, respectively; $p < 0.05$), whereas toxic chemical concentrations in infants were higher than those in the mothers. With respect to the within-individual intraclass correlation coefficient (ICC), the first morning void (FMV) of the mothers had high ICCs for all chemicals (range: 0.72–0.99), except for BPA, monobenzyl phthalate (MBzP), and monocarboxyoctyl phthalate (MCOP). The ICC values of most chemicals were moderate to high (range: 0.34–0.99) in the first morning void. However, there were different patterns of ICCs in the infants. These findings indicate the importance of mother–infant pair studies and the necessity of research in infants, as they have different exposure sources and pathways from adults.

Keywords: first morning void; mother–infant pair; spot urine; variability

1. Introduction

Chemicals enter the human body via the ingestion of food, dermal absorption from the skin, and inhalation from air [1]. After entering the human body, most chemicals are metabolized and excreted in urine within a few hours or days [2,3]. A group vulnerable to the short- and long-term effects of toxic chemicals due to a lack of data on health status, access to environmental information, and ability to cope with environmental pollution is termed an environmentally vulnerable group [4]. Fetuses and infants are considered environmentally vulnerable because their metabolism is incompletely developed

compared that of adults, making it difficult to release toxic chemicals from the body effectively [5,6]. In general, fetuses, neonates, and infants are physically dependent on their mothers, and therefore their health is closely related to their mothers' health [7]. The findings of Tratnik et al. and Bamai et al. further support this view, based on the measurements of bisphenol A (BPA) and phthalate metabolites among family members [8,9]. They reported that the urine concentrations of BPA and phthalate metabolites were significantly correlated in mothers and children but not in fathers and children. Thus, health information of infants must be collected in conjunction with that of their mothers.

Mother–child pair-based research of urine concentrations of phthalate metabolites, BPA, triclosan (TCS), and parabens has been conducted in several countries, with the median concentrations of phthalate metabolites and environmental phenols ranging from 0.2 to 755.0 and 0.2 to 98.3 μg/L [8–23]. These studies have reported that the concentrations of toxic chemicals in the mothers are highly correlated with those in their children and that the levels in children were higher than those in the mothers [8,9,12,16,23]. The higher concentrations of toxic chemicals in children have been attributed to their relatively small body size, mouth sucking, contact with plastic toys, and incomplete metabolism [12,24]. This pattern is assumed to be higher in younger children, that is, infants, necessitating studies on urine concentrations of toxic chemicals in mother–infant pairs.

Phthalate diesters that enter the human body are hydrolyzed in the intestine to monoesters, which are then absorbed. Furthermore, these monoester metabolites are usually oxidized in the body, excreted in urine largely as glucuronide conjugates with a half-life of less than 12 h [15,18,25,26]. Bisphenol A is rapidly metabolized as conjugated BPA-glucuronide by the liver and excreted in the urine with a half-life of less than 6–7 h [27,28]. After absorption, parabens and TCS are converted to p-hydroxybenzoic acid and glucuronic acid, respectively, and excreted in urine as free or glucuronide conjugated with a half-life of less than 13–29 h [18,29,30]. These findings suggest that the presence of toxic chemicals in urine indicates recent exposure, that is, within the last few hours or a day [11,18]. Therefore, urine is more effective than other matrices, such as blood, to identify recent exposure of humans to these chemicals [3,31].

Non-persistent chemicals with a short half-life may differ in concentration in the body depending on the exposure event or sampling time [3,31]. Even in samples from the same subject, temporal variations such as inter- and intra-day variations may exist [3,27,29,31–36]. Thus, the single-spot urine data obtained from a cross-sectional study can underestimate or overestimate the risks with regard to chemical exposure and incorrectly assess the health effects [3,31]. Therefore, serial biomonitoring is necessary to identify any variations in the concentration of non-persistent chemicals. Several studies have reported between- or within-variability in phthalate metabolites, BPA, TCS, and parabens [3,27,29,31–36]. However, the subjects of these studies were mainly pregnant women or adults, and there are no studies measuring variability in mothers and their infants. Information on individual variability can provide insights into toxic chemical metabolism and a basis for judging whether the concentration data are more reliable. Therefore, in this study, we aimed to (a) assess the exposure concentration of phthalate metabolites, BPA, TCS, and parabens in mothers and their infants; (b) identify the potential correlation in the exposure levels between the mothers and their infants; and (c) assess the within-individual variability in phthalate metabolites, BPA, TCS, and parabens in the mothers and their infants.

2. Materials and Methods

2.1. Study Population and Sample Collection

The present study is a follow-up study involving the prospective examination of an association between 15 toxic chemicals and lifestyles in the breast milk of Korean postpartum women [6]. The inclusion criteria were as follows: (1) mothers who participated in a study that analyzed the concentration of toxic chemicals in mothers' breast milk in 2018, (2) mothers who spent the majority of the time during the day with their infants, and (3) mothers who understood the purpose of

the study and provided written consent. The exclusion criteria were mothers and infants having metabolic disturbances or abnormal urine excretion. Urine sampling and individual interviews with the participants were conducted from 10 to 28 June 2019. Qualified nurses collected 20 mL of urine samples from the mothers and their infants, and the collected samples were stored in polypropylene tubes, which did not contain toxic chemicals, at −70 °C until further analysis. For serial monitoring, urine samples were collected from nine mothers three times a day for 1 week: first morning void (FMV; 6–9 a.m.), lunch-time void (LV; 12–3 p.m.), and bed-time void (BV; 10 p.m.–12 a.m.). Urine samples were collected from the infants once a day in the morning. Finally, 225 samples were collected from 45 mothers and 71 samples were collected from 36 infants. For the variability analysis, 189 and 42 samples were collected from the mothers and their infants, respectively.

A questionnaire addressing the following aspects was answered by the mothers via face-to-face interviews: demographic characteristics (maternal age, maternal BMI, residence area, education status, household monthly income, and employment status), infant characteristics (gender, age, and weight), consumption of food for the last 1 week (meat, dairy, fish, fast-food, ice-cream, and canned food), used household goods (new furniture, PVC, air freshener, plastic, and plastic food container), and behavior (passive smoking). This study was reviewed and approved by the Institutional Review Board of Kyung Hee University (KHSIRB-18-029-1).

2.2. Analysis of Chemicals

To determine the exposure levels of chemicals in the study subjects, 5 environmental phenols [BPA, methyl paraben (MP), ethyl paraben (EP), propyl paraben (PP), and TCS] and 10 phthalate metabolites [mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP), mono-N-butyl phthalate (MnBP), mono-isobutyl phthalate (MiBP), mono-(2-ethyl-5-carboxypentyl) phthalate (MECPP), monobenzyl phthalate (MBzP), mono ethyl phthalate (MEP), mono (2-ethylhexyl) phthalate (MEHP), mono-isononyl phthalate (MiNP), and mono carboxy octyl phthalate (MCOP)] were quantitatively analyzed in urine samples.

The chemical analysis was conducted in two phases: first analysis of 5 phenols (BPA, TCS, and three parabens) and then 10 phthalate metabolites. Analytical procedures were as previously reported and applied by the national biomonitoring programs [37,38]. Chemical analysis was conducted in the laboratory where the chemical analysis of urine environmental phenols and phthalate metabolites of the Korean National Biomonitoring Program (Korean National Environmental Health Survey, KoNEHS) is being conducted. All urine samples were collected in alcohol-washed specimen cups. For the analysis of urine environmental phenols, 1 mL of each quality-controlled substance and urine sample was collected and placed in a glass container. Then, 0.25 mL of isotope-labeled internal standards (13C-BPA, D4-MP, D4-EP, D4-PP, and 13C-TCS; Sigma-Aldrich, Merck, NJ, USA), 0.20 mL of enzyme (β-glucuronidase), and 10.00 mL of buffer solution (ammonium acetate) were mixed and reacted for 16 h. For sample preparation, liquid–liquid extraction (LLE) was applied using 6 N hydrochloric acid, potassium carbonate, and solvents. After concentrating the samples, samples with nitrogen for 20 min at 45 °C, they were eluted with 0.3 mL 10% acetonitrile and used for further analysis. Urine concentrations of environmental phenols were determined using a high-performance liquid chromatography–triple tandem mass detector (HPLC-MS/MS, API Triple Quad 550 System; AB SCIEX, Concord, ON, Canada). For phthalate metabolites, 0.50 mL of the samples was used for the quantitative analysis. For environmental phenols, LLE was applied and the internal standards (13C-MEHHP, 13C-MEOHP, 13C-MnBP, 13C-MiBP, 13C-MECPP, 13C-MBzP, 13C-MEP, 13C-MEHP, 13C-MiNP, and 13C-MCOP; Cambridge Isotope Laboratories, Tewksbury, MA, USA), hydrochloric acid, and solvents were used; the experimental equipment used was HPLC-MS/MS (Xevo-TQ-XS, Waters, MA, USA).

Analytical procedures were conducted following a strict internal quality assurance protocol by measuring a procedural blank and internal quality control (QC) urine sample for each batch of measurements. The internal QC was performed before the analysis of whole samples, and it included

the tests of linearity, accuracy, precision, and detection limit. In the linearity test, R2 was 0.999 in the calibration curve with seven points of the concentration range in pooled urine. The accuracy test was performed using Standard reference materials (National Institute of Standards & Technology, Gaithersburg, MD, USA, NIST 3672—organic contaminants in smoker's urine and NIST 3673—organic contaminants in non-smoker's urine) and yielded recovery rates of ±15% and coefficient of variations of ≤5% for all analytes of environmental phenols and phthalate metabolites. The limit of detection (LOD) was as follows: BPA, 0.015 μg/L; MP, 0.172 μg/L; EP, 0.114 μg/L; PP, 0.118 μg/L; TCS, 0.039 μg/L; MEHHP, 0.139 μg/L; MEOHP, 0.154 μg/L; MnBP, 0.282 μg/L; MiBP, 0.188 μg/L; MECPP, 0.113 μg/L; MBzP, 0.082 μg/L; MEP, 0.131 μg/L; MEHP, 0.139 μg/L; MiNP, 0.043 μg/L; and MCOP, 0.091 μg/L. The external QC followed the German External Quality Assessment Scheme in which urine chemicals passed from the 57th to 63rd (2017–2019; urine BPA, TCS, MEHHP, MECPP, MEOHP, MnBP, MiBP, MBzP, and MEHP). Creatinine level was measured using the kinetic colorimetric assay (rate-blanked and compensated) with CREA (Roche, Indianapolis, IN, USA) reagent on the Hitachi 7600 machine (Hitachi, Tokyo, Japan).

2.3. Statistical Analysis

Statistical analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC, USA) and MedCalc 19.2.1 (MedCalc Software Ltd., Ostend, Belgium). For values below the LOD, we assigned the value of LOD divided by the square root of 2 (Hornung and Reed, 1990). The concentrations of environmental phenols and phthalate metabolites (μg/L) in urine were used for the statistical analyses to correct for urine dilution. In accordance with the WHO criterion, spot urine samples with a creatinine concentration lower than 300 mg/L or higher than 3000 mg/L were excluded from the analysis [11,39]. The normality of distribution was tested using the Shapiro–Wilk test. Spearman correlation coefficients between maternal and infant samples were calculated.

For the variability analysis, intraclass correlation coefficient (ICC) values were estimated by measuring the chemicals in repeated urine samples collected over several hours and days and by calculating between-individual variance divided by the total variance [3,40]. Values for ICC ranged from 0 to 1. ICC values close to 0 indicate poor reproducibility, in which all variations are due to variability within the subject, whereas values close to 1 indicate a high reproducibility, in which all variations are due to variability between subjects [3,36,41]. An ICC of more than 0.75 indicates a high reproducibility, and that of 0.40–0.75 indicates moderate reproducibility and less than 0.4 indicates low reproducibility [42]. The FMV was defined as the first sample collected from each participant during a day. This sample reflects the dietary status of the previous 24 h period. Subsequently, urine sampling was performed at lunch-time and bed-time, every day for 1 week. Exposure duration was defined as time from post-FMV to pre-FMV on the following day [31,35]. The ICC values of within-individual (FMV, LV, BV, and all spot samples) were estimated for mothers and those of all spot samples were calculated for infants.

3. Results

3.1. Characteristics of the Study Population

The participants were aged between 25 and 37 (mean 31) years, with the pre-pregnancy body mass index (BMI) of the mothers ranging between 17.5 and 29.7 (mean 21.3) kg/m^2. The majority of mothers lived in non-metropolitan areas (57.8%); a total of 93.3% of them had a college degree or higher and 77.8% were employed. The mean infant age and weight (range) were 11 (6–14) months and 9.8 (7.6–12.5) kg, respectively. The majority of the infants (86.7%) were female (Table 1).

Table 1. General characteristics of the study populations.

Characteristic	Category	N (%)/Mean (SD)	Median (range)
Maternal age (years)		30.9 (2.8)	31 (25–37)
Maternal BMI (m^2/kg)		21.4 (2.7)	20.8 (17.5–29.7)
Residence area	Metropolitan	19 (42.2)	
	Non-Metropolitan	26 (57.8)	
Maternal education	<College	3 (6.7)	
	≧College	42 (93.3)	
Household income (USD/month)	<5000	26 (57.8)	
	≧5000	19(42.2)	
Employment status	Yes	35 (77.8)	
	No	10 (22.2)	
Infant sex	Male	6 (13.3)	
	Female	39 (86.7)	
Infant age (month)		11.4 (1.5)	12.0 (6–14)
Infant weight (kg)		9.8 (1.2)	9.6 (7.6–12.5)
Infant birth weight (kg)		2.8 (0.3)	3.1 (2.2–3.4)
Breastfeeding period (months)		7.5 (3.9)	8 (1–13)

BMI, body mass index; SD, standard deviation.

3.2. Concentration of the Chemicals in the Mothers and Infants

Phthalate metabolites (MEP, MnBP, MiBP, MBzP, MiNP, MEHP, MEOHP, MEHHP, MECPP, and MCOP) in the mothers and infants were detected in 60–100% and 42–91% of the creatinine-adjusted urine samples, respectively, with the median concentrations of 0.53–26.2 and 0.81–61.8 μg/L. BPA, TCS, and parabens (MP, EP, and PP) in the mothers and infants were detected in 59–100% and 44–87% in the creatinine-adjusted urine samples, with the median concentrations of 0.24–76.3 and 2.06–12.5 μg/L (Table 2). The median concentrations of phthalate metabolites, BPA, TCS, MP, and PP in the infants were higher than those in the mothers (Figure 1).

Table 2. Concentration of chemicals in mothers and infants (μg/L).

Parent Compound	Measured Biomarker	LOD	Mother (n = 45), Samples (n = 225)							Infant (n = 36), Samples (n = 71)							
			% > LOD	GM	Percentile					% > LOD	GM	Percentile					
					SD	Min	25th	50th	75th	Max			SD	Min	25th	50th	75th	Max
Creatinine-adjusted data (μg/L)																		
DEP	MEP	0.13	65	3.94	7.19	< LOD	< LOD	3.68	4.71	3693	42	9.81	15.75	< LOD	< LOD	< LOD	24.7	199
DnBP	MnBP	0.28	100	25.5	2.03	4.23	14.6	26.2	41.8	138	91	64.4	5.20	< LOD	34.6	61.8	100	1241
DIBP	MiBP	0.19	100	6.59	3.24	0.21	2.92	5.68	11	145	90	19.7	6.34	< LOD	7.91	16.4	38.1	1009
BBzP	MBzP	0.08	60	0.66	4.38	< LOD	< LOD	0.63	1.36	43.3	44	1.89	6.79	< LOD	< LOD	< LOD	4.75	15.6
DINP	MiNP	0.04	100	1.02	2.45	0.07	0.28	0.53	0.99	57.6	91	0.85	2.40	< LOD	0.49	0.81	1.3	6.08
DEHP	MEHP	0.14	100	2.68	2.24	0.29	1.66	2.79	4.63	259	89	3.63	3.29	< LOD	2.14	3.62	5.98	40.5
	MEOHP	0.15	94	4.25	3.38	< LOD	2.68	4.88	6.62	302	84	11.8	7.20	< LOD	9.62	14.3	20.6	81
	MEHHP	0.14	97	7.9	2.89	< LOD	6.25	9.7	13	557	87	14.76	6.25	< LOD	11.56	26.12	42.1	104.62
	MECPP	0.11	97	10.1	3.26	< LOD	6.87	11.2	15.8	533	91	40.8	3.52	< LOD	27.4	41.4	67.8	300
	MCOP	0.09	97	2.3	2.88	< LOD	1.31	2.18	3.71	121	81	6.85	7.85	< LOD	4.84	7.68	12.9	58.2
	BPA	0.02	66	1.54	11.58	< LOD	< LOD	1.57	3.6	29.2	87	6.39	9.12	< LOD	3.42	6.8	13.2	59.5
	TCS	0.04	75	0.32	5.18	< LOD	0.09	0.24	1.15	5.44	82	2.19	6.81	< LOD	0.92	2.06	4.67	78.7
	MP	0.17	100	6.16	2.90	0.94	2.92	4.85	9.97	464	93	27.9	9.17	< LOD	7.08	12.5	51.8	9192
	EP	0.11	99	65.6	6.45	< LOD	22.1	76.3	208	4692	44	19.6	8.58	< LOD	< LOD	< LOD	79.4	807
	PP	0.12	59	0.84	6.12	< LOD	< LOD	0.51	2.7	65.8	84	3.84	8.97	< LOD	0.82	2.08	11.9	2431
Unadjusted data (μg/L)																		
DEP	MEP	0.13	65	5.02	8.96	< LOD	< LOD	4.68	8.37	1499	44	6.22	20.04	< LOD	< LOD	< LOD	19.2	95.9
DnBP	MnBP	0.28	100	32.1	3.25	2.72	17	32.1	59.4	315	95	27.8	6.98	< LOD	12.2	32.4	71.3	824
DIBP	MiBP	0.19	100	8.31	3.15	0.24	3.47	7.65	18.3	302	95	9.11	7.30	< LOD	3.92	8.57	20.7	281
BBzP	MBzP	0.08	60	0.93	5.08	< LOD	< LOD	0.91	1.76	104	47	1.11	6.43	< LOD	< LOD	< LOD	2.32	9.86
DINP	MiNP	0.04	100	0.69	2.73	0.07	0.37	0.66	1.2	73	98	0.38	3.26	< LOD	0.17	0.29	0.85	6.65
DEHP	MEHP	0.14	100	3.38	2.69	0.18	1.98	3.55	6.29	264	94	1.66	3.11	< LOD	0.78	1.7	2.98	33.6
	MEOHP	0.15	94	9.33	3.22	< LOD	3.31	6.51	10	309	88	5.56	7.78	< LOD	2.75	7.56	13.8	45
	MEHHP	0.14	97	18.6	4.62	< LOD	6.51	12.8	19.6	569	91	9.66	8.04	< LOD	4.96	12.2	22.5	72.7
	MECPP	0.11	97	13.1	3.82	< LOD	7.13	15.7	23.5	545	96	17.6	4.63	< LOD	8.47	21.4	38.3	129
	MCOP	0.09	97	2.96	3.50	< LOD	1.61	2.82	5.28	154	85	3.49	7.94	< LOD	1.34	4.39	9.29	27.3
	BPA	0.02	66	2.17	14.50	< LOD	< LOD	2.27	5.49	76.2	92	2.88	10.66	< LOD	1.63	3.69	5.57	52.3
	TCS	0.04	75	0.49	5.25	< LOD	0.14	0.4	1.78	10.1	87	0.92	7.04	< LOD	0.45	0.96	2.15	17.7
	MP	0.17	100	21.2	4.81	0.77	3.82	6.68	12	1537	98	11.9	9.22	< LOD	1.81	6.86	30.5	4915
	EP	0.11	99	83.2	8.81	< LOD	26.2	103	288	3447	45	72.1	9.38	< LOD	< LOD	< LOD	84.7	807
	PP	0.12	59	1.09	7.73	< LOD	< LOD	0.61	3.37	218	89	35	7.55	< LOD	0.39	0.66	4.34	639

GM, geometric mean; LOD, limit of detection; SD, standard deviation; MEP, mono ethyl phthalate; MnBP, mono-N-butyl phthalate; MiBP, mono-isobutyl phthalate; MBzP, monobenzyl phthalate; MiNP, mono-isononyl phthalate; MEHP, mono (2-ethylhexyl) phthalate; MEOHP, mono-(2-ethyl-5-oxohexyl) phthalate; MEHHP, mono-(2-ethyl-5-hydroxyhexyl) phthalate; MECPP, mono-(2-ethyl-5-carboxypentyl) phthalate; MCOP, mono carboxy octyl phthalate; BPA, bisphenol A; TCS, triclosan; MP, methyl paraben; EP, ethyl paraben; PP, propyl paraben.

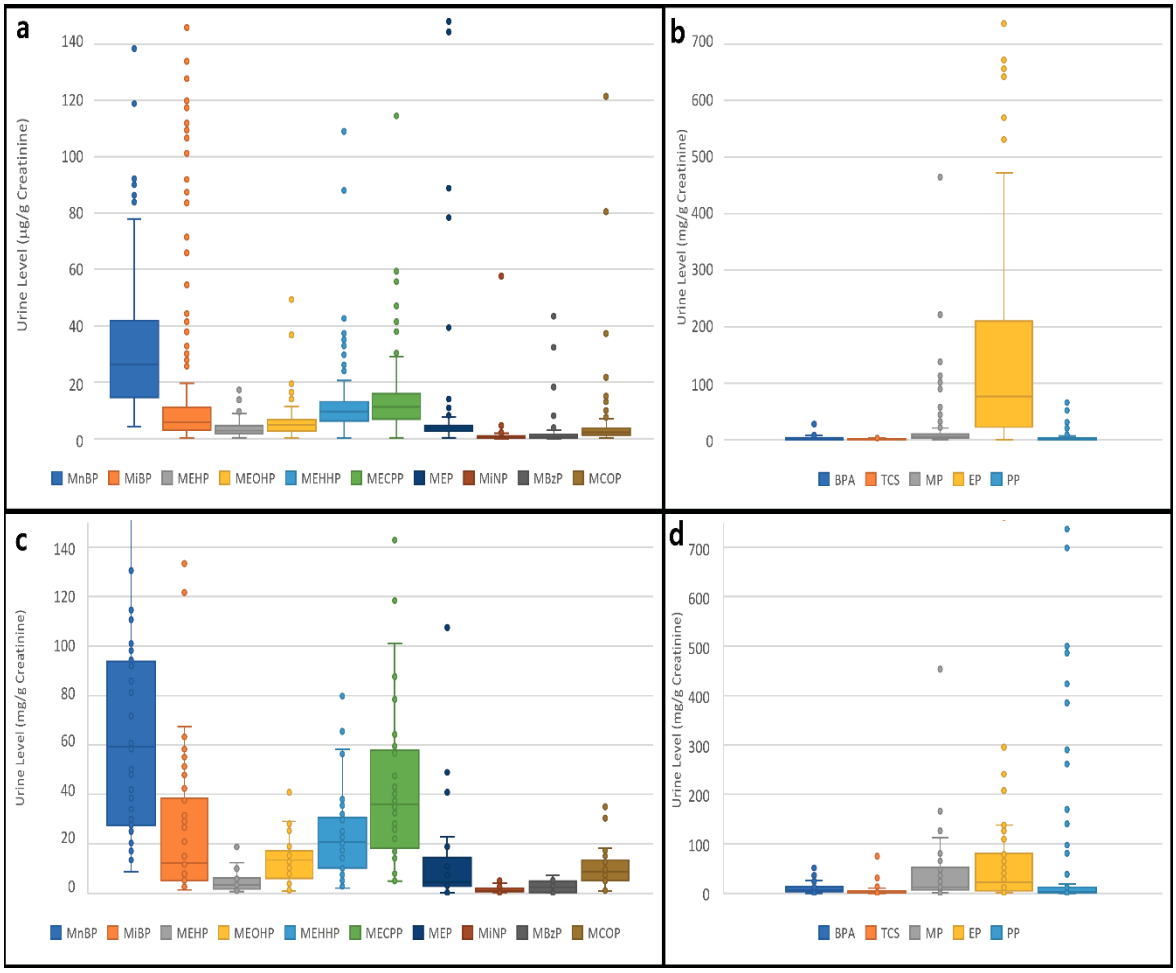

Figure 1. Creatinine-adjusted concentrations of chemicals in spot urine sample. (**a**) Concentration of creatinine-adjusted phthalate metabolite in mothers, (**b**) concentration of creatinine-adjusted BPA, TCS, and paraben in mothers, (**c**) concentration of creatinine-adjusted phthalate metabolites in infants. (**d**) Concentration of creatinine-adjusted BPA, TCS, and paraben in mothers. MnBP, mono-N-butyl phthalate; MiBP, mono-isobutyl phthalate; MEHP, mono (2-ethylhexyl) phthalate; MEOHP, mono-(2-ethyl-5-oxohexyl) phthalate; MEHHP, mono-(2-ethyl-5-hydroxyhexyl) phthalate; MECPP, mono-(2-ethyl-5-carboxypentyl) phthalate; MEP, mono ethyl phthalate; MiNP, mono-isononyl phthalate; MBzP, monobenzyl phthalate; MCOP, mono carboxy octyl phthalate; BPA, bisphenol A; TCS, triclosan; MP, methyl paraben; EP, ethyl paraben; PP, propyl paraben.

3.3. Correlations between the Mothers and Infants for the Chemical Concentrations

The concentrations of MEP, MnBP, MiBP, and BPA in the mothers were positively correlated with those in the infants (0.45, 0.612, 0.89, and 0.51, respectively, $p < 0.05$; Table 3).

3.4. Variability in Chemicals in Mothers and Infants

The urine concentrations of phthalate metabolites, BPA, TCS, MP, EP, and PP for one week in the mothers and their children are presented in Figures 2 and 3. The number of urine samples of nine mothers and seven infants was 189 and 42, respectively. The number of FMV, LV, and BV samples was 63 each. The age of the mothers ranged between 28 and 37 (mean 32) years, and that of infants was 10 (6–13) months, and the infants' mean weight was 9.1 (7.6–10.3) kg.

Table 3. Spearman's correlation coefficients of phthalate metabolites, BPA, TCS, and parabens in creatinine-adjusted urine samples.

(μg/L)	I-MEP	I-MnBP	I-MiBP	I-MBzP	I-MiNP	I-MEHP	I-MEOHP	I-MEHHP	I-MECPP	I-MCOP	I-BPA	I-TCS	I-MP	I-EP	I-PP
M-MEP	0.45 *	0.03	0.05	0.01	0.01	0.03	0.04	0.01	0.11	0.23	0.09	0.05	0.10	0.01	0.07
M-MnBP	0.02	0.62 **	0.25	0.19	0.17	0.15	0.10	0.11	0.18	0.09	0.31	0.08	0.25	0.01	0.01
M-MiBP	0.26	0.38 *	0.89 **	0.20	0.10	0.25	0.30	0.37 *	0.35	0.08	0.02	0.03	0.03	0.07	0.02
M-MBzP	0.03	0.10	0.06	0.05	0.30	0.31	0.09	0.04	0.31	0.22	0.25	0.01	0.19	0.39 *	0.31
M-MiNP	0.04	0.13	0.26	0.16	0.09	0.13	0.21	0.29	0.22	0.07	0.18	0.18	0.44 *	0.15	0.01
M-MEHP	0.01	0.17	0.03	0.12	0.05	0.04	0.04	0.02	0.12	0.01	0.30	0.08	0.27	0.10	0.10
M-MEOHP	0.06	0.07	0.03	0.26	0.04	0.14	0.01	0.02	0.07	0.28	0.41 *	0.01	0.50 *	0.04	0.06
M-MEHHP	0.01	0.12	0.02	0.26	0.10	0.19	0.06	0.03	0.01	0.21	0.33	0.02	0.50 *	0.07	0.02
M-MECPP	0.06	0.03	0.03	0.30	0.01	0.05	0.03	0.03	0.10	0.19	0.41 *	0.02	0.55 **	0.02	0.11
M-MCOP	0.02	0.11	0.17	0.02	0.09	0.11	0.13	0.18	0.17	0.05	0.22	0.03	0.53 *	0.07	0.04
M-BPA	0.20	0.29	0.22	0.08	0.04	0.18	0.25	0.26	0.32	0.08	0.39 *	0.24	0.19	0.25	0.15
M-TCS	0.10	0.16	0.11	0.07	0.48 *	0.52 *	0.24	0.25	0.22	0.05	0.51 *	0.27	0.02	0.09	0.08
M-MP	0.07	0.25	0.07	0.03	0.17	0.01	0.21	0.19	0.11	0.13	0.05	0.09	0.01	0.16	0.15
M-EP	0.15	0.13	0.08	0.21	0.09	0.23	0.35	0.38 *	0.24	0.11	0.17	0.16	0.10	0.17	0.12
M-PP	0.29	0.16	0.17	0.36 *	0.14	0.08	0.17	0.19	0.14	0.14	0.01	0.04	0.12	0.32	0.32

M-, mothers; I-, infants; MEP, mono ethyl phthalate; MnBP, mono-N-butyl phthalate; MiBP, mono-isobutyl phthalate; MBzP, monobenzyl phthalate; MiNP, mono-isononyl phthalate; MEHP, mono (2-ethylhexyl) phthalate; MEOHP, mono-(2-ethyl-5-oxohexyl) phthalate; MEHHP, mono-(2-ethyl-5-hydroxyhexyl) phthalate; MECPP, mono-(2-ethyl-5-carboxypentyl) phthalate; MCOP, mono carboxy octyl phthalate; BPA, bisphenol A; TCS, triclosan; MP, methyl paraben; EP, ethyl paraben; PP, propyl paraben. * $p < 0.05$, ** $p < 0.001$.

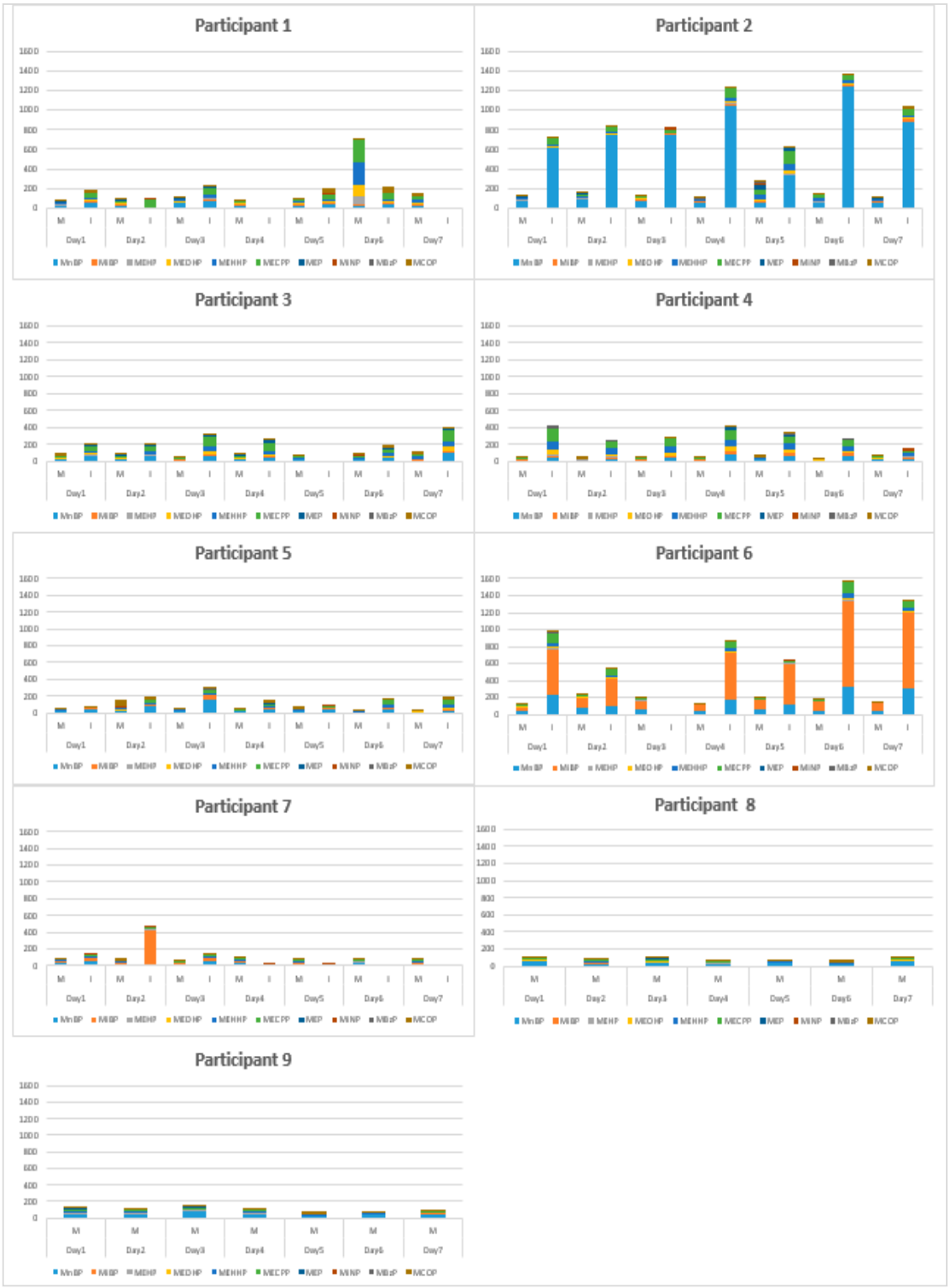

Figure 2. Serial monitoring of phthalate metabolites for 1 week in mothers and infants. M, mother; I, infant; MEP, mono ethyl phthalate; MnBP, mono-N-butyl phthalate; MiBP, mono-isobutyl phthalate; MBzP, monobenzyl phthalate; MiNP, mono-isononyl phthalate; MEHP, mono (2-ethylhexyl) phthalate; MEOHP, mono-(2-ethyl-5-oxohexyl) phthalate; MEHHP, mono-(2-ethyl-5-hydroxyhexyl) phthalate; MECPP, mono-(2-ethyl-5-carboxypentyl) phthalate; MCOP, mono carboxy octyl phthalate.

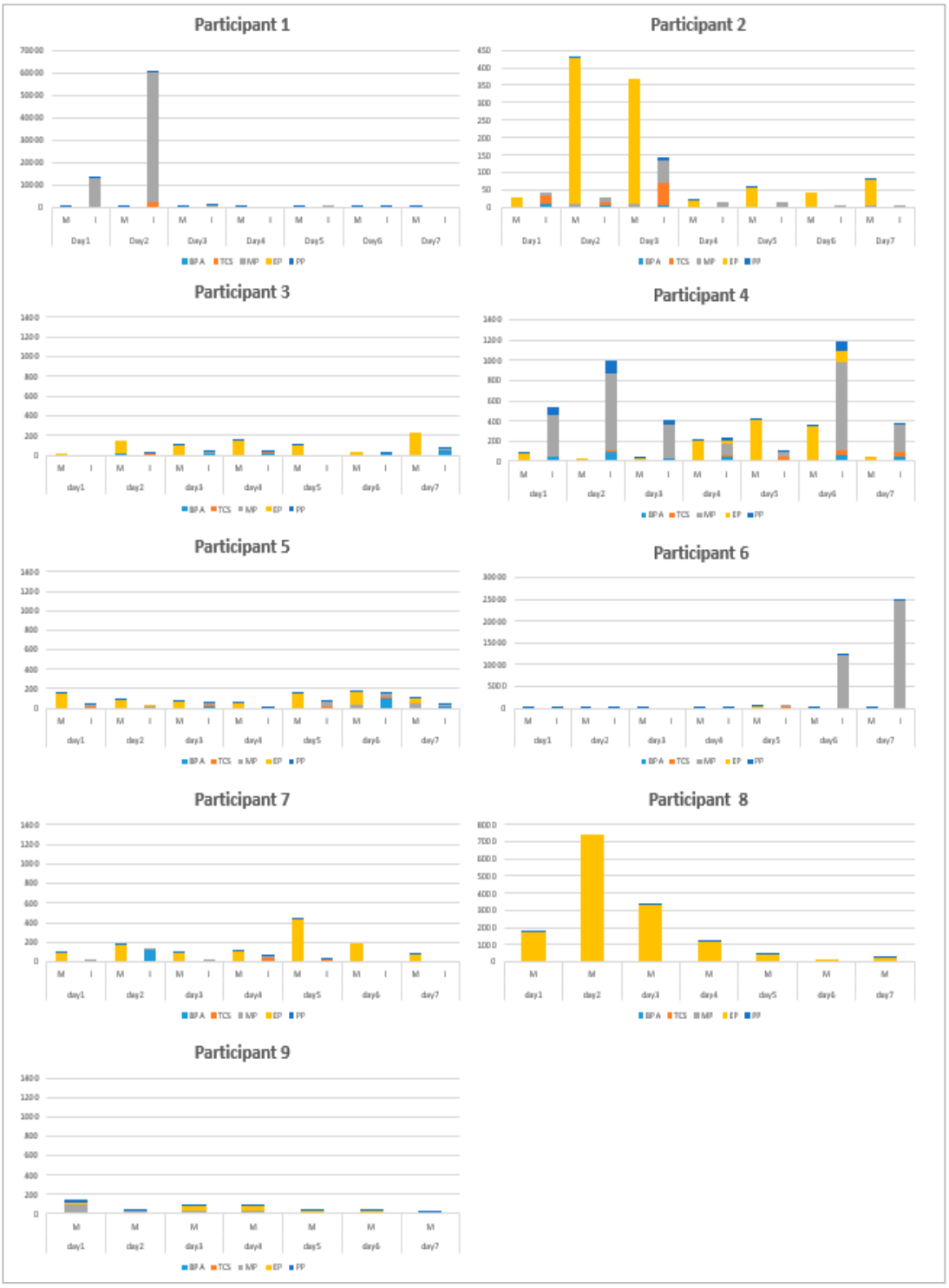

Figure 3. Serial monitoring of BPA, TCS, and parabens for 1 week in mothers and infants. M, mother; I, infant; BPA, bisphenol A; TCS, triclosan; MP, methyl paraben; EP, ethyl paraben; PP, propyl paraben.

For within-individual ICC, the FMV of the mothers had high ICCs for all chemicals (range: 0.72–0.99), except for BPA, MBzP, and MCOP. The LV and BV of the mothers' samples had low ICCs (range: 0.04–0.67) for most chemicals, except for MnBP, MiBP, TCS, and PP. The spot samples of the mothers had low ICCs for most chemicals, whereas those of the infants had high ICCs (range: 0.70–0.96) for most chemicals, except for MEP, TCS, MP, and PP (Table 4).

Table 4. Variability in the concentrations of phthalate metabolites, BPA, TCS, and parabens in creatinine-adjusted urine samples.

	Within-Individual ICC (95% CI)				
Creatinine Adjusted Data (μg/L)	**M-FMV (*n* = 63)**	**M-LV (*n* = 63)**	**M-BV (*n* = 63)**	**M-SPOT (*n* = 189)**	**I-SPOT (*n* = 35)**
MEP	0.82 (0.55 to 0.95)	0.12 (0.08 to 0.77)	0.80 (0.51 to 0.95)	0.17 (0.02 to 0.57)	0.57 (0.29 to 0.92)
MnBP	0.94 (0.86 to 0.99)	0.92 (0.80 to 0.98)	0.85 (0.64 to 0.96)	0.90 (0.84 to 0.95)	0.96 (0.87 to 0.99)
MiBP	0.99 (0.98 to 0.99)	0.97 (0.93 to 0.99)	0.98 (0.94 to 0.99)	0.98 (0.97 to 0.99)	0.93 (0.80 to 0.99)
MBzP	0.34 (0.13 to 0.83)	0.41 (0.15 to 0.85)	0.49 (0.05 to 0.87)	0.38 (0.06 to 0.68)	0.83 (0.48 to 0.97)
MiNP	0.72 (0.31 to 0.93)	NA	0.39 (0.05 to 0.84)	NA	0.68 (0.05 to 0.94)
MEHP	0.85 (0.64 to 0.96)	0.13 (0.05 to 0.77)	0.77 (0.44 to 0.94)	0.15 (0.06 to 0.56)	0.91 (0.73 to 0.98)
MEOHP	0.86 (0.65 to 0.96)	0.14 (0.03 to 0.77)	0.18 (0.03 to 0.78)	0.14 (0.07 to 0.56)	0.90 (0.70 to 0.98)
MEHHP	0.77 (0.44 to 0.94)	0.13 (0.05 to 0.77)	0.09 (0.05 to 0.76)	0.13 (0.09 to 0.55)	0.93 (0.78 to 0.99)
MECPP	0.72 (0.32 to 0.93)	0.16 (0.07 to 0.78)	0.02 (0.01 to 0.74)	0.16 (0.04 to 0.56)	0.83 (0.48 to 0.97)
MCOP	0.38 (0.02 to 0.84)	0.26 (0.03 to 0.81)	0.34 (0.03 to 0.83)	0.27 (0.05 to 0.62)	0.83 (0.48 to 0.97)
BPA	0.40 (0.09 to 0.84)	0.29 (0.06 to 0.81)	NA	0.26 (0.05 to 0.62)	0.70 (0.12 to 0.94)
TCS	0.94 (0.86 to 0.99)	0.94 (0.84 to 0.98)	0.93 (0.84 to 0.98)	0.94 (0.89 to 0.97)	NA
MP	0.78 (0.45 to 0.94)	0.46 (0.14 to 0.86)	0.64 (0.11 to 0.90)	0.55 (0.24 to 0.77)	0.38 (0.16 to 0.88)
EP	0.72 (0.30 to 0.93)	0.62 (0.06 to 0.90)	0.74 (0.37 to 0.93)	0.67 (0.44 to 0.83)	0.86 (0.74 to 0.82)
PP	0.91 (0.79 to 0.98)	0.85 (0.63 to 0.96)	0.65 (0.14 to 0.90)	0.76 (0.58 to 0.87)	NA

ICC, intraclass correlation coefficient; M-FMV, maternal first morning void; M-LV, maternal lunch-time void; M-BV, maternal bed-time void; NA: not available; MEP, mono ethyl phthalate; MnBP, mono-N-butyl phthalate; MiBP, mono-isobutyl phthalate; MBzP, monobenzyl phthalate; MiNP, mono-isononyl phthalate; MEHP, mono (2-ethylhexyl) phthalate; MEOHP, mono-(2-ethyl-5-oxohexyl) phthalate; MEHHP, mono-(2-ethyl-5-hydroxyhexyl) phthalate; MECPP, mono-(2-ethyl-5-carboxypentyl) phthalate; MCOP, mono carboxy octyl phthalate; BPA, bisphenol A; TCS, triclosan; MP, methyl paraben; EP, ethyl paraben; PP, propyl paraben.

4. Discussion

In this study, we attempted to measure the concentrations of 15 toxic chemicals in urine samples and identify the variability in these chemicals in Korean mothers and infants by serial monitoring.

Phthalate metabolites, BPA, TCS, and parabens have high variability in urine concentrations due to their short half-lives and varying metabolic changes that depend on the source and route of exposure [33,43]. Several studies have reported the variability in these chemicals in urine, indicating variable reproducibility in phthalate metabolites, BPA, TCS, and parabens [3,27,29,31–34,36,44–46]. In our study, the urine FMV ICCs were high for most chemicals except for BPA, MBzP, and MCOP. In contrast, the urine ICCs of spot samples were high for MnBP, MiBP, TCS, and PP, suggesting that FMV displayed higher reproducibility. These results agree with findings from Koch et al. in which they reported that the ICCs were higher during repeated 24-h composites than for spot samples [31]. The urine BPA ICC (spot and FMV) was low (0.26–0.40), an observation that agrees with numerous studies (0.14–0.26) [27,31,32,34,44–46]. The urine TCS ICC (spot and FMV) was high (0.94–0.94), which is similar to the results (0.96) from Koch et al. [31]; however, the ICC value was moderate (0.47–0.61) in other studies [34,44,45]. The urine parabens (MP, EP, and PP for both spot and FMV) ICCs were moderate to high (0.55, 0.67, 0.76/0.78, 0.72, and 0.91, respectively), which agrees with findings from previous studies [34,44,45]. The urine ICCs (spot and FMV) of MEP, MBzP, MiNP, MEHP, and secondary metabolites were variable (0.01–0.38 and 0.34–0.86, respectively), except for those of MnBP and MiBP (0.90–0.99), which reflect similar findings from Townsend et al. [46]. In this study, the variability of chemicals in the urine from infants and mothers was confirmed. To the best of our knowledge, variability in urine with phthalate metabolites, BPA, TCS, and parabens in infants has never been reported. Therefore, it is difficult to compare the ICCs obtained in the present study with those of other studies. When compared with those reported in adults, the ICC of infants showed a different pattern. For example, the ICCs of BPA and EP in infants were higher than those in the mothers, whereas the ICCs of TCS in infants was lower than that in the mothers. As the metabolism and elimination of chemicals vary depending on the exposure dose, species, and age, more research on the variability in urine from infants is required [8,11].

The concentrations of phthalate metabolites, BPA, parabens, and TCS in the urine samples from the Korean mothers and their infants were lower than or comparable with those in previous studies on mother–child pairs (Table 5). Specifically, the median concentrations of MEP, MiBP, MBzP, MiNP, TCS, MP, and PP were 3.68, 5.68, 0.63, 0.53, 0.24, 4.85, and 0.51 μg/L, respectively, which were lower than the values reported from Denmark, Germany, Greece, Ireland, Japan, Poland, Slovakia, Spain, Sweden, and Taiwan [9,10,12–21]. The median concentrations of BPA, MnBP, MEHP, and secondary metabolites of phthalate (MEOHP, MEHHP, MECPP, and MCOP) were slightly lower or higher than the values reported from Greece, Ireland, Japan, Poland, Slovakia, Spain, Sweden, and Taiwan [8–10,12–22]. These patterns were similar to the concentrations of these toxic chemicals in infants. However, the median concentrations of EP in mothers and their infants were 76.3 and 21.8 μg/L, respectively, which were higher than the values reported from Denmark, Greece, Spain, and Sweden [10,15,18,20]. A relatively high urine concentration of EP in Koreans has also been reported in a population-based cross-sectional study and a few regional studies, in which the median concentration of EP in women and children ranged from 29.2–44.6 and 2.9–23.6 μg/L, respectively [42,47,48]. The Korean National Environmental Health Survey (2017) further supports this finding, that is, the mean concentration of EP in adults and infants was 39.3 and 17.4 μg/L, respectively [49]. This pattern is presumed to be because the Korean population has a unique exposure pattern compared with that in other countries, such as preferred diet, medicine, cosmetics, personal care product use, and regulatory policy [48]. For example, the Ministry of Food and Drug Safety (FDA) of Korea permits the use of EP as a preservative of food and cosmetic, despite the prohibition on the usage of parabens as a preservative in other countries [50,51]. In this study, the median concentrations of BPA and TCS in infants were also higher than the values reported in previous studies [8,10,11,13,15,18,20]. This can also be attributed to relaxed regulatory policies on toxic chemicals in Korea. For example, restriction policies of the European Union (EU) have been implemented for BPA use in baby bottle, food packing, and thermal papers, and BPA is recognized as an endocrine disruptor [52–57]. However, it was not until 2019 that BPA use was banned for packing products used for infants and toddlers in Korea [51]. The US Food and Drug Administration banned TCS from washing products in 2016 and hospital products in 2019 [58,59]. However, the Korean FDA permits the use of TCS below the human safety standard (0.3% in the product for cleaning) [51]. Considering the fact that the concentrations of EP, BPA, and TCA in urine are high in Koreans, as reported in several studies, more detailed studies on the source of exposure and the route of exposure are needed.

In this study, the concentration of toxic chemicals in infants was higher than that in the mothers except EP, and this pattern was similar to those observed in previous studies [9,10,12,13,15–19]. A Spanish study reported that the MECPP concentration in children was four times higher than that in mothers, and another study also reported that the plasma BPA concentration in newborn infants was 11 times higher than that in adults when the same weight-normalized dose was used in a physiology-based toxicokinetic (PBTK) model [9,60]. The reason for this pattern is presumed to be associated with physiological characteristics, as infants and young children have a lower metabolic rate than adults and the liver detoxification process might not be fully developed in children [5,6,61]. This suggests that even when exposed to the same dose of toxic chemicals, children are more harmed than adults, and therefore TDI research and stricter regulation for children, infants, and neonates are needed [6,12]. In this study, the concentrations of MEP, MnBP, MiBP, and BPA in mothers were significantly correlated with those in infants, similar to those reported previously [8,11,15–17,20]. However, Tratnik et al. reported that the urine concentrations of BPA in mother–child pairs were significantly correlated, whereas those between fathers and their children were not correlated [23]. In addition, the urine BPA concentrations in children aged 6–8 years were higher than those of children aged 9–11 years, suggesting age-dependent variability in toxic chemical concentrations [8,11,37,62,63]. Therefore, it is necessary to collect the data of mothers and infants in pairs and educate them, because the mother and child live together in the same space with the same dietary intake and lifestyle. More detailed studies are needed on sources and pathways of exposure to toxic chemicals in children.

Table 5. Comparison of urine concentrations of phthalate metabolites, BPA, TCS, and paraben among mother–children pair studies.

Authors (Publication Year)	Country (*n*)	Mother (*n*)/Infant (*n*)	MEP	MnBP	MiBP	MBzP	MiNP	MEHP	MEOHP	MEHHP	MECPP	MCOP	BPA	TCS	MP	EP	PP
This study (2020)	South Korea (n = 159)	Mother (225)	3.68	26.2	5.68	0.63	0.53	2.79	4.88	9.7	11.2	2.18	1.6	0.2	4.9	76	1
		Infants (71)	12.2	61.8	16.4	3.26	0.81	3.62	14.3	22.7	41.4	7.68	6.8	2.1	13	22	2
Hlisníková et al. (2019) [16]	Slovakia (n = 78)	Parents (n = 21)	24.1	32.82	17.1			3.26	7.63	10.03	5.6						
		Children (n = 57)	23.7	54.11	32.1			2.32	14.5	17.52	11.73						
Tratnik et al. (2019) [8]	Slovenia (n = 381)	Mother (n = 155)											1.1				
		Children (n = 155)											1.9				
		Father (n = 71)											0.2				
Cullen et al. (2017) [12]	Ireland (n = 240)	Mother (n = 120)	50.2 **	18.5 **	23.8 **	3.1 **		2.8 **	8.8 **	17							
		Children (n = 120)	38.7 **	26.1 **	41.4 **	5.4 **		3.5 **	17.7 **	32.8							
Covaci et al. (2015) [11]	Six European states	Mother (n = 639)											1.94 *				
		Children (n = 653)											1.96 *				
Cutanda et al. (2015) [13]	Spain (n = 240)	Mother (n = 120)	150.8 **	30.59 **	35.03 **	7.99 **	9.52 **	6.65 **	12.96 **	20.07 **			1.97 **				
		Children (n = 120)	198.9 **	50.95 **	61.38 **	13.9 **	15.13 **	6.85 **	24.28 **	38.36 **			2.01 **				
Bamai et al. (2015) [9]	Japan (n = 303)	Mother (n = 125)		<LOD	47.3 *	11.6 *		28.6 *	47.3 *		7.5 *						
		School-age (n = 178)		<LOD	47 *	16.3 *		19.7 *	51.5 *		34.9 *						
Myridakis et al. (2015) [20]	Greece (n = 478)	Mothers (n = 239)	134	36.1	39.2	6		7.6	17.6	25.7			1.2		98	3	
		Children (n = 239)	34.4	23.9	34.4	6.5		2.8	20	30.5			2.1		17	93	
Larsson et al. (2014) [18]	Sweden (n = 196)	Mothers (n = 98)	37	58.49		10.83		2.4	7.34	13.17	10.04		1.2	<LOD	40	2	14
		Children (n = 98)	27.4	83.24		22.37		3.19	17.74	26.69	23.12		1.5	<LOD	5.5	1	2.1

Table 5. *Cont.*

Authors (Publication Year)	Country (*n*)	Mother (*n*)/Infant (*n*)	MEP	MnBP	MiBP	MBzP	MiNP	MEHP	MEOHP	MEHHP	MECPP	MCOP	BPA	TCS	MP	EP	PP
Polinski et al. (2014) [21]	Poland (*n* = 313)	3rd Preg (*n* = 165)	22.7	4.6	11.1			0.2	1.6	2.73							
		Children (*n* = 148)	9.8 *	4 *	2.5 *			0.2 *	1.2 *	2.1 *							
Enke et al. (2013) [14]	Germany (*n* = 18)	Mothers (*n* = 9)	61.4 *	14.3 *	15.3 *			3.3 *	4.8 *	5.6 *	10.4 *						
		Newborn (*n* = 9)	11.4 *	22.5 *	6.5 *			0.9 *	1.3 *	1.7 *	11.9 *						
Frederiksen et al. (2013) [15]	Denmark (*n* = 288)	Mothers (*n* = 145)	29	21	37			1.7	6.2	13	8.7		2.1	0.7	16	1	
		Children (*n* = 143)	19	33	58			2.2	11	22	16		1.9	0.5	2.9	0	<LOD
Song et al. (2013) [22]	South Korea (*n* = 657)	Mothers (*n* = 265)						10.9	25.9	29.6							
		Children (*n* = 392)						20.9	116.6	115.2							
Kasper-Sonnenberg et al. (2012) [17]	Germany (*n* = 208)	Mothers (*n* = 104)	53.8 *	30.9 *	43 *	6.3 *		4.6 *	12.9 *	17.3 *	20.5 *						
		Children (*n* = 104)	33.6 *	54.2 *	68.7 *	11.7 *		4 *	26.4 *	31 *	42.1 *						
Casas et al. (2011) [10]	Spain (*n* = 150)	Preg (*n* = 120)	324	27.5	29.9	10.5		4.4	15.7	17.3	32.20	4	2.2	6.1	191	9	30
		Children (*n* = 30)	755	30.2	41.9	33		6.2	44.6	57.4	115	7.5	4.2	1.2	150	8	22
Lin et al. (2011) [19]	Taiwan (*n* = 189)	Preg (*n* = 100)		87.49	15.2	2.07		16.37	29.5	33.2	44.69						
		5 yrs old (*n* = 59)		154.53	54	7.64		21.38	58.71	60.05	131.86						
		2 yrs old (*n* = 30)		314	51	11.25		21.04	114.33	150.85	202.62						

* non-creatinine-adjusted value (unadjusted); ** geometric mean value. MEP, mono ethyl phthalate; MnBP, mono-N-butyl phthalate; MiBP, mono-isobutyl phthalate; MBzP, monobenzyl phthalate; MiNP, mono-isononyl phthalate; MEHP, mono (2-ethylhexyl) phthalate; MEOHP, mono-(2-ethyl-5-oxohexyl) phthalate; MEHHP, mono-(2-ethyl-5-hydroxyhexyl) phthalate; MECPP, mono-(2-ethyl-5-carboxypentyl) phthalate; MCOP, mono carboxy octyl phthalate; BPA, bisphenol A; TCS, triclosan; MP, methyl paraben; EP, ethyl paraben; PP, propyl paraben; LOD, limit of detection; Preg, pregnancy; yrs, years.

The strength of this study is that the concentrations of the 15 toxic chemicals, including phthalate metabolites, BPA, TCS, and parabens, were analyzed in urine samples from mothers and their children in pairs. While most previous studies were conducted in children aged more than 5 years, we collected urine samples from infants. In addition, within-individual variability in these chemicals was estimated in urine samples from mothers and their infants, and we compared variability in the FMV, LV, BV, and spot samples. The results of this study can be used as a reference for future studies. However, the study does have some limitations: as selected populations are not representative of the Korean population, caution should be exercised when generalizing these results. Another limitation is the small sample size, which restricted our ability to make conclusions regarding causal relationships.

5. Conclusions

In this study, we attempted to measure the concentrations of 15 toxic chemicals in urine samples and identify the variability in these chemicals in Korean mothers and their infants by serial monitoring. The concentrations of phthalate metabolites, BPA, parabens, and TCS in the urine of the Korean mothers and infants were lower than or comparable with those reported previously, except EP, in mother–child pair research. The reason for the relatively high urine concentration of EP in Koreans is due to population-based unique exposure patterns, such as dietary and lifestyle factors. The concentration of toxic chemicals in the infants was higher than that in the mothers, and the concentrations were significantly correlated with those in the infants. With respect to within-individual variability, FMV had a higher reproducibility than the LV, BV, and spot samples. The ICC values of most chemicals were moderate to high. However, patterns of ICCs differed in the infants. These findings demonstrate the importance of mother–infant pair study and the necessity for research in infants, as they have different exposure sources and exposure pathways from adults.

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Conflicts of Interest: The authors declare no conflict of interest.

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